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# Summary Overview of Health Effects Associated with Chloroprene Health Issue Assessment

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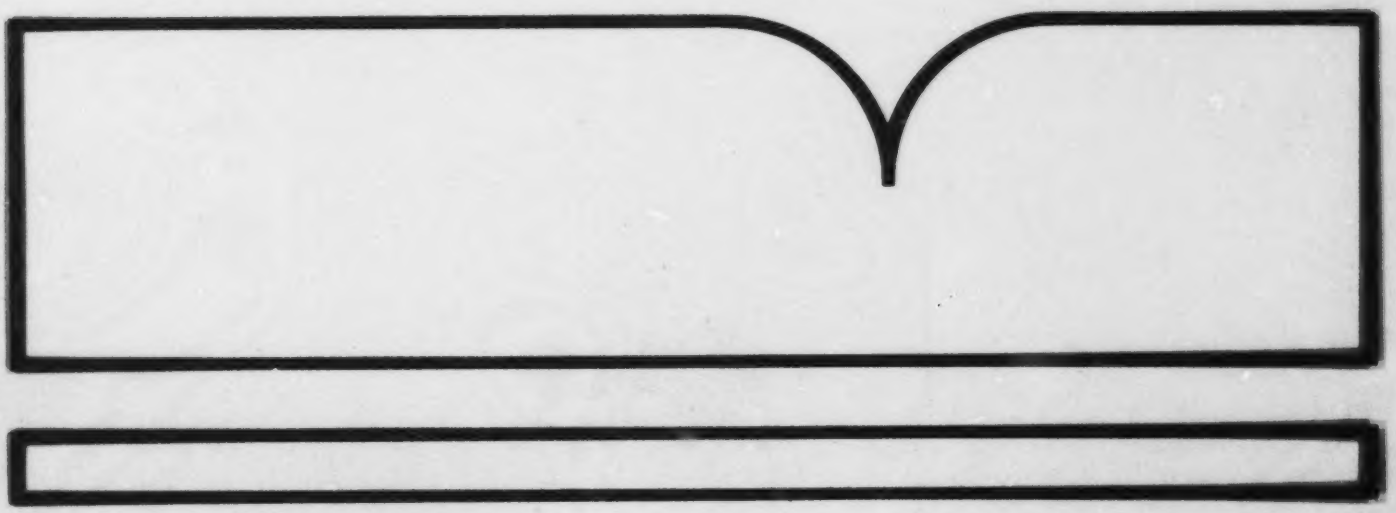

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# Summary Overview of Health Effects Associated with Chloroprene:

## Health Issue Assessment

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16. ABSTRACT

The purpose of this report is to summarize available information concerning possible health effects associated with exposure to chloroprene. Emphasis has been placed on reviewing the available information useful for determining whether or not chloroprene affects human health at air concentrations which might be encountered by the general public under ambient conditions. This summary addresses the acute and chronic toxicity, reproductive effects, mutagenicity, and carcinogenicity of chloroprene. Also discussed is background information on air quality aspects of chloroprene, inclusing sources, distribution, and fate.

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# I. INTRODUCTION

The purpose of this paper is to summarize available information concerning possible health effects associated with exposure to chloroprene. Emphasis has been placed on reviewing the available information useful for determining whether or not chloroprene affects human health at air concentrations which might be encountered by the general public under ambient conditions. This summary addresses the acute and chronic toxicity, reproductive effects, mutagenicity, and carcinogenicity of chloroprene. Also discussed is background information on air quality aspects of chloroprene, including sources, distribution, and fate.

Chloroprene, a monomer used in the manufacture of synthetic rubber, is a volatile and highly reactive chemical, with an estimated residence time in the atmosphere of 4.8 hours. Chloroprene affects the liver and the hematopoietic, circulatory, immune, and nervous systems at high levels of acute exposure. Limited epidemiological studies of rubber workers in the Soviet Union have indicated a possible association between exposure to chloroprene and cancer of skin and lung. However, limited epidemiological studies of U.S. workers have not confirmed this association. There are needs for research in epidemiology, chronic toxicity, and pharmacokinetics of chloroprene as well as for measurement of chloroprene concentrations in the atmosphere.

## II. AIR QUALITY

Chloroprene (2-chloro-1,3-butadiene) is a flammable, volatile liquid with an ether-like odor. It is soluble in alcohol, and from an industrial perspective appears to be slightly soluble in water. Chloroprene is a highly reactive electrophile and will autocatalytically combine with oxygen, polymerize spontaneously at room temperature, and react with a wide variety of organic and inorganic chemicals.

Chloroprene is currently produced in the United States by gas-phase chlorination of butadiene to dichlorobutene, followed by distillation and dehydrohalogenation with aqueous sodium hydroxide to chloroprene. Facilities for the commercial production of chloroprene are located in the United States, the Federal Republic of Germany, Northern Ireland, France, Japan, and the U.S.S.R. No estimates are available of the number of persons exposed to chloroprene during its manufacture and use, however, 4.7 million people live within 50 kilometers of chloroprene facilities (Cote, 1985). In 1976, U.S. production was reported to be 164 million kg (361 million lb); in 1977, world production was estimated to have been 300 million kg (660 million lb) (International Agency for Research on Cancer, 1979). A more recent report (49FR 46938, November 29, 1984) places the annual world production of chloroprene at approximately $1.2 \times 10^8$ megagram (254 million lb).

Table 1 lists the sites where chloroprene is produced. DuPont also uses chloroprene transported from La Place, LA at a facility in Louisville, KY which would be a source of air emissions.

Chloroprene's only known use is in the manufacture of polychloroprene elastomers. Solid elastomer, also known as neoprene synthetic rubber, is used in the automotive industry for tubing, belts, and gaskets, in the construction industry, in the manufacture of wire and cable jackets, and consumer goods. Liquid or latex elastomers are used in adhesives and as fabric coatings.

Chloroprene is manufactured by a continuous process in a closed system; however, because such a system includes valves, piping, and reactor vessels, the possibility for fugitive emissions exists. Also, venting of chloroprene vapors to the atmosphere may occur during cleaning and maintenance of the system. Releases may occur during loading and unloading when chloroprene is transported to other sites for elastomer production, during transfer from storage tanks by pipeline, or in the process of manufacturing neoprene.

Chloroprene is a highly volatile liquid (vapor pressure 181 mm Hg @ 20°C) and therefore can be expected to volatilize quickly under normal environmental conditions. Estimated values of the evaporative half-life of chloroprene in water under experimental conditions based on the method of Dilling (1977) indicated a rapid evaporation of chloroprene from water under natural conditions.

Chloroprene's fate in the environment depends on chemical degradative processes as well as degradation or accumulation in biological systems. Cupitt (1980) describes two chemical removal processes in air that affect organic compounds, such as chloroprene, that contain double bonds. The first is reaction with ambient hydroxyl radicals which add across the double bonds of chloroprene to form compounds such as aldehydes, ketones, and dicarbonyls. Halogenated organics such as chloroprene tend to lose halogen atoms in the form of halo-oxy radicals.

The second chemical removal process is reaction with ozone (ozonolysis), which results in the formation of a carbonyl (aldehyde or ketone) and a

*Table 1. Chloroprene Producers and Captive Users*

| Company | Location | 1984 Capacity (M lb) | 1984 Production (M lb) |
|---|---|---|---|
| DuPont | La Place, LA | 275 | 240 |
| DuPont | Louisville, KY | -- | -- |
| Denka | Houston, TX | 60 | 48 |
| Conoco | Houston, TX | -- | 1.7[a] |
| Total | | 335 | 289.7 |

*Source: Serenbetz, 1985; Henkson, 1985*
[a]*Chloroprene produced as by-product.*

percarbonyl biradical that may undergo further rearrangement to form, for example, organic acids and carbon dioxide. Although the rate of the ozone reaction is much lower than that of the hydroxyl reaction, the former may have an equal influence on atmospheric levels because the levels of ozone are much greater than that of the hydroxyl radical. According to Cupitt (1980) the calculated atmospheric residence time for chloroprene, defined as the time required for the concentration to be reduced to 1/e (approximately 37%) of its initial value, is 0.2 days (4.8 hrs). Physical processes are unlikely to have significant roles in the removal of chloroprene from the atmosphere.

No published reports were found in which levels of chloroprene in the environment were determined. There are limited data from industrial hygiene monitoring of the workplace, indicating that the occurrence of chloroprene in the atmosphere near manufacturing and processing facilities is a possibility, but quantification of these atmospheric emissions is lacking. Detectable chloroprene concentrations are only likely in the ambient air in proximity to emission sources involved in high volume production or use of the chemical. Measurements made in Deer Park, TX by Pellizzari et al. (1979) ranged from 266-4000 ng/m$^3$.

# III. HEALTH EFFECTS

No studies were found on the absorption or distribution of chloroprene following inhalation, oral, or dermal exposure. From the observation of toxic effects in humans and animals after acute exposure via these routes, it can be inferred that absorption can occur from the lungs, gastrointestinal tract, and skin. An approximation of chloroprene's systemic distribution can be made by considering the organs showing injury after acute or subchronic exposure. Organs affected include the liver, lungs, spleen, central nervous system, kidneys, epicardium, testes, and bone marrow. Based on several *in vivo* and *in vitro* studies and its structural similarity to vinyl chloride, the metabolism of chloroprene is likely to involve the hepatic mixed-function oxidase system and the production of epoxide intermediates (Agadzhanov et al., 1973; Shukuryan, 1967; Bartsch, 1977; Bartsch et al., 1979). Detoxification involves glutathione and results in the excretion of conjugates in the urine (Summer and Greim, 1980).

## 1. Systemic Toxicity In Humans

Reported symptoms due to acute human exposure to high concentrations of chloroprene include headache, irritability, dizziness, insomnia, fatigue, respiratory irritation, cardiac palpitations, chest pains, gastrointestinal disorders, dermatitis, temporary hair loss, conjunctivitis, and corneal necrosis (International Agency for Research on Cancer, 1979). Toxic effects in humans from acute high-level chloroprene exposures have been reported for the liver, circulatory system, hematopoeitic, central and peripheral nervous systems, immune system, reproductive system, and the periodontium. Chloroprene has also been reported to cause chromosomal aberrations in humans, and exposure of workers has been linked in some studies to an increased incidence of skin and lung cancer. Levels of exposure causing symptoms and clinical signs have not generally been well defined, and there are conflicting reports concerning many of the clinical and epidemiological findings (International Agency for Research on Cancer, 1979).

Exposure of human subjects to chloroprene vapors at ~3500 mg/m$^3$ causes giddiness and nausea in less than 15 minutes (Nystrom, 1948). The odor threshold is ~ 500 mg/m$^3$.

Symptoms of chronic exposure (to 200 to 1230 mg/m$^3$) in rubber workers were fatigue, pressure and pain in the chest, giddiness, and irritability. Dermatitis and hair loss were observed in some cases. Symptoms usually appeared about one month after initial exposure to these high levels of chloroprene and were less severe after a weekend without exposure. EKGs showed no abnormalities (Nystrom, 1948).

A biochemical and hematological evaluation of workers exposed to chloroprene (Gooch and Hawn, 1981) showed no significant statistical differences in any of the parameters measured, compared with controls. However, Ward et al. (1981) suggested that exposure to chloroprene vapor associated with neoprene production may contribute to liver function abnormalities.

Soviet scientists (Sanotskii, 1980; Volkova et al., 1976) reported adverse effects on reproduction (functional disturbances in spermatogenesis and increased spontaneous abortions in wives of exposed workers) in workers exposed to chloroprene. However, insufficient details are available in the reports to adequately evaluate the results.

The Sanotskii (1980) study presents interpretational difficulties concerning the level of participation of the exposed workers and their wives, the quantitative interpretation of the reported sperm abnormalities, and the appropriate matching of exposed and control populations. As embryos with chromosome abnormalities are spontaneously aborted very early in pregnancy, the chances that a retrospective questionnaire such as that used in this study would have discovered a real increase in the rate of spontaneous abortion are remote. In addition to the problem of recall bias, nearly three-quarters of these chromosomally abnormal embryos are expelled at the time of the normally expected menses. This minimizes any woman's ability to document embryonic loss. It has been reported that only 15-20% of the abortions that occur during pregnancy can be documented by recall under the best of circumstances. Also, it is strongly suggested that most abortions occur (in excess of 60%) at the time of first-expected menses. Reporting bias during this early gestational period is especially damaging to any meaningful interpretation of this report. Thus it is not reasonable to draw conclusions on the possible effect of chloroprene on early fetal losses from the use of the method in this report. Also, the very low rate of reported miscarriages for both exposed individuals (9.3%) and controls (5.4%) suggests that marked underreporting took place.

In addition, in view of the large number of males available for sperm analysis, the 9.5% participation (15/143) indicates that a considerable degree of selection bias may have been present. Males with reproductive problems may have self-selected themselves to the detriment of meaningful interpretation. Had a representative or larger sample been enlisted, a different picture might have emerged. For the above reasons, it is not possible to interpret this study with any degree of reliability.

## 2. Systemic Toxicity In Animals

Since chloroprene exposure occurs primarily via inhalation, most of the reported animal studies on chloroprene have used this route of exposure. Few such studies have been reported from the U.S.; most have been performed in the USSR, and several have been performed in the Scandinavian countries. The Soviet animal toxicology studies explored male and female reproductive impacts of chloroprene in the ppm or $mg/m^3$ range (1ppm = 3.6 $mg/m^3$ at 25@C and 760 mm Hg). The Soviet literature on studies of chronic chloroprene exposure in male rats reports a decreased number of spermatogonia and a decline in sperm motility, as well as an increased number of dead sperm, at exposure levels as low as 0.15 $mg/m^3$ (0.04 ppm). Female rats exposed via inhalation to chloroprene were reported to have increased embryonal mortality, with decreased birth weights of pups at levels of exposure of approximately 3 $mg/m^3$ (approximately 1ppm). Continuous exposures throughout gestation at levels as low as 0.13 $mg/m^3$ (~ 0.04 ppm) also were reported to show a significant elevation in embryonal mortality, with a "no observed effect level" (NOEL) of 0.056 $mg/m^3$ (0.015 ppm). Except for male reproductive effects at approximately 0.01 ppm, the Soviet literature emphasizes a NOEL of slightly below 0.1 ppm (0.6 ppm is the 1977 USSR recommendation for threshold limit value).

In contrast to the USSR studies, a U.S. study (Culik et al., 1978), where careful attention has been paid to the purity of the chloroprene, maternal toxicity and fetotoxicity have been reported only at levels of 25 ppm or above. The Soviet literature has only limited descriptions of the procedures used to produce and characterize the chloroprene exposure atmospheres, but reproductive effects were consistently reported in the range of 1-10 ppm. However, the problem of contaminant by-product effects needs to be evaluated. The complex effects of chloroprene and its by-products on reproduction are

important, and, depending upon synthetic and exposure conditions, may vary. Thus, the actual exposure atmosphere used in the studies becomes critical in any evaluation of the USSR studies.

Animal toxicity studies with chloroprene indicate that high-level exposures by inhalation, gavage, or subcutaneous injection affect the liver, lungs, kidneys, and central nervous system (CNS). The effects include vascular congestion in most organs examined; hepatic centrilobular necrosis, degeneration, and repair; degeneration of the renal tubular epithelium; lung edema; CNS depression; and ultimately death. Oxidized chloroprene was more toxic than the unoxidized test material in several species (Nystrom, 1948), and fasted rats were more sensitive to the toxic effect of chloroprene than were fed rats (Aznauryan et al., 1981).

Table 2 summarizes the information on the effects caused by inhalation of chloroprene vapor by rats and the doses at which they occurred. Two studies showed toxic effects at low exposure concentrations (Salnikova and Fomenko, 1973; Davtyan, 1972). In the study by Aznauryan et al. (1981) a group of animals given a high-protein diet plus amino acid supplementation did not show the effects of chloroprene exposure as did those animals on a normal diet and at the same exposure level.

Two studies (Fichidzhyan and Zil'fyan, 1976; Agakhanyan, 1982) reported that chloroprene exposure by subcutaneous injection was associated with reduced antibody production and suppression of the transplantation rejection reaction in rats; also, germinal centers of the spleen and lymph nodes showed hypoplasia and atrophy.

Based on the available information, the liver appears to be the primary target organ of chloroprene toxicity in animals, following high levels of exposure regardless of the route of exposure. Glutathione conjugation appears to be a major detoxification pathway (Clary et al., 1978). However, there is some indication of a more subtle systemic toxicity in that both immunocompetence and behavioral changes, such as extinction of conditioned reflexes, were affected by chloroprene exposure.

Liver regeneration and repair were reported during the longer term inhalation studies (4 to 6 months) of chloroprene. Chronic (~ 2 yr) inhalation studies of well characterized chloroprene atmospheres are needed to adequately address the systemic toxicity of chloroprene.

## 3. Carcinogenicity In Animals and Man

The evaluation of carcinogenicity of chemicals such as chloroprene depends heavily on animal bioassays and any available epidemiologic evidence. However, other factors, including mutagenicity, metabolism (particularly in relation to interaction with DNA), and pharmacokinetic behavior, have an important bearing on both the qualitative and quantitative assessment of carcinogenicity.

Zil'fyan and Fichidzhyan (1972) studied the effect of chloroprene in 60 white mixed-breed mice, each weighing about 18-20 g. Thirty mice were subcutaneously injected with 0.1 mg peach oil per 1 g body weight, and the other 30 mice were injected with peach oil and a Crocker murine sarcoma tumor suspension. Increased tumor growth (2 times in diameter and 4 to 5 times in weight) was found after chloroprene administration into mice before and after transplantation of the Crocker murine sarcoma. The report suggests that this effect of chloroprene was related to an immunodepressant activity of the chloroprene.

Three series of skin application studies were conducted by Zil'fyan et al. (1977). In these studies, three groups of random-bred mice received dermal application of 50% chloroprene in benzene twice weekly for 25 weeks, 0.1%

*Table 2. Effects on Rats from Subchronic Inhalation Exposure to Chloroprene*

| Exposure Level | Duration | Effect |
|---|---|---|
| 171 $mg/m^3$ | 6 hr/day/5 days/wk for 4 wks | Increased mortality, changes in relative weight of kidney, liver, and lungs. (Clary et al., 1978). |
| 100 $mg/m^3$ | 4 hr/day for 5 mo | Fatty degeneration of liver, effects on renal tubules and glomeruli, and on myocardium (Aznauryan et al., 1981). |
| 44 $mg/m^3$ | 6 hr/day, 5 days/wk for 4 wks | Eye irritation, restlessness, nasal discharge, hair loss. Increased mortality, growth retardation, and liver damage. Lung hemorrhages and edema in animals that died. (Clary et al., 1978). |
| 30 $mg/m^3$ | 5 hr/day for 7 mo | Extinction of conditioned reflexes (Airapetyan and Matevosyan, 1973). |
| 30 $mg/m^3$ | 5 hr/day, 6 days/wk for 6 mo | Irreversible changes in histopathology of adrenal gland and anterior pituitary (Markaryan and Shakhlamov, 1975a, 1975b). |
| 11 $mg/m^3$ | 6 hr/day, 5 days/wk for 4 wks | Skin and eye irritation and weight loss in rats and hamsters. (Clary et al., 1978). |
| 3 $mg/m^3$ | Dams exposed during gestation | Decrease in spontaneous motor activity in 2-mo.-old progeny (Salnikova and Fomenko, 1973). |
| <2 $mg/m^3$ | 4 hr/day for 5.5 mo | CNS depression, decrease in $O_2$ demand and liver function (male rats) (Davtyan, 1972). |
| 1 $mg/m^3$ | 5 hr/day, 6 days/wk for 6 mo | Reversible changes in adrenal cortex (Markaryan and Shakhlamov, 1975 |

9,10-dimethyl-1,2-benzanthracene (DMBA) in benzene twice weekly for 25 weeks, or 50% chloroprene solution in benzene twice weekly for 25 weeks followed by five skin treatments with 0.01% DMBA in benzene. Of 100 mice treated with 50% chloroprene, 58 survived 6 months, and 37 survivors were killed at 18 months. In the eighty mice that were painted with 0.1% DMBA alone, skin carcinomas appeared in 55 of 60 animals alive. Times to tumor formation were not reported. Forty-two of 80 mice treated with chloroprene and 0.01% DMBA survived for 6 months. No skin or other tumors were reported. Because of a lack of experimental detail in this study, a conclusive evaluation of the results is not possible.



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In a study by Zil'fyan et al. (1975), 100 random-bred albino rats were dosed by gavage twice weekly with chloroprene at 200 mg/kg in sunflower oil for 25 weeks. Forty rats survived for 2 years. No tumors were observed. However, chloroprene was reported to be carcinogenic when administered intratracheally at 200 mg/kg to 100 random-bred albino rats at 20-day intervals until the animals had received five treatments, with an observation period of 14 months. It is difficult to draw definite conclusions from this study because the experiment was of insufficient duration and was not reported in adequate detail (International Agency for Research on Cancer, 1979).

At the end of 2 years, no local sarcomas were observed in 100 random-bred albino rats given 10 subcutaneous injections of 400 mg chloroprene/kg and in 100 rats given 50 subcutaneous injections of 200 mg/kg of chloroprene in sunflower oil (Zil'fyan et al., 1977). Eighty-eight rats survived in the former group and 46 in the latter group for 6 months or more. Among 60 rats injected with single doses of DMBA at 0.5 mg/animal, 50 survived to the appearance of first tumor (3.5 months), and 32 (64%) of these 50 animals developed local sarcomas. Sixty rats received single injections of 0.5 mg DMBA into the left flank and 50 subcutaneous injections of chloroprene at 200 mg/kg into the right flank. Local sarcomas (site not specified) were observed in 24 of these rats.

Ponomarkov and Tomatis (1980) studied the carcinogenicity of chloroprene. In this experiment, chloroprene (100 mg/kg body weight) dissolved in olive oil was administered in single oral doses to female DBIV rats on the 17th day of pregnancy, and their progeny (89 males and 90 females) received weekly doses of 50 mg/kg 0.3 mL olive oil. Fourteen control female DBIV rats received 0.3 ml olive oil on the 17th day of pregnancy, and their progeny (53 males and 53 females) were given 0.3 mL olive oil weekly for life, beginning at weaning. All survivors were killed at 120 weeks or when moribund. All animals were autopsied and internal organs were examined histologically. In chloroprene-treated male rats, several tumor types were observed that were not seen in controls. Although subcutaneous fibromas were more numerous in chloroprene-treated males than in controls, the total incidence of tumors was similar in chloroprene-treated and control rats. The authors concluded that the use of other species and, possibly, administration by inhalation, would be necessary before the carcinogenicity of chloroprene could be fully assessed.

Menezes et al. (1979) used an established cell line (ICP) derived from the hamster lung for the purpose of detecting the possible transforming capability of chloroprene *in vitro*. After 17 generations in culture, the cells were treated with chloroprene (purity 99%, contained 0.8% of chloro-1-butadiene) at concentrations of 1, 10, and 100 mg/ml for 42 days. The treated and untreated cells were transplanted subcutaneously into newly born hamsters or, using the intraocular tract, into adult hamsters. The cells not treated with chloroprene did not produce any tumors after transplantation. Those treated with 1 mg/mL of chloroprene produced tumors at 14 weeks after transplantation. Treatment with higher concentrations (10 and 100 mg/mL) did not accelerate the transformation process. Untreated cells did not produce any tumors even with transplantation of $1 \times 10^6$ cells. The cells treated with chloroprene (1 to 100 mg/mL) produced tumors with transplantation of as low as $1 \times 10^4$ cells. These tumors were fibrosarcomas, and some of them showed a very high degree of malignancy. The cells treated with the lowest concentration (1 mg/mL) had the strongest transformation characteristics. The author concluded that as chloroprene is mutagenic, the results obtained in these *in vitro* transformation studies were not surprising.

Only limited epidemiological studies from chloroprene-exposed workers are available. Five reports of epidemiologic studies have been reported, but these are based on data obtained from only three populations. In one population

(Yerevan, USSR), cancer morbidity was studied (Khachatryan, 1972a, 1972b). In the other two populations (both Du Pont plants in the United States), only mortality data were collected (Pell, 1978, 1980; Leet and Selevan, 1982).

Analyses of lung cancer and skin cancer occurrence in an industrial region of the USSR (Yerevan) suggest an increased risk of each of these cancers among persons working with chloroprene or its derivatives (Khachatryan, 1972a, 1972b). However, the lack of information on potentially important confounding variables, as well as the brevity and lack of clarity in the description of the study design, make the evaluation of the results very difficult and subject to error. More rigorous epidemiologic exploration of this large data set might prove highly productive and should be encouraged.

Analyses of two cohorts of DuPont workers exposed to chloroprene at the Chambers and Louisville Works (Pell, 1978, 1980; Leet and Selevan, 1982) also provided suggestive evidence of a slightly increased risk of lung cancer death. While this finding is consistent with that of Khachatryan, drawbacks in both study designs preclude definitive conclusions. As recommended by the NIOSH report on chloroprene (Leet and Selevan, 1982), the Louisville Works data set should be expanded to include men who terminated before the present study's enrollment date of 1957. This action would not only increase the sample size but would also remove a potentially major bias in the death rates. That bias may be obscuring a greater excess of lung cancer deaths among workers exposed to chloroprene than is currently evident in the reports that have been prepared to date.

In summary, the evidence for human carcinogenicity of chloroprene must be classified as either very limited or inadequate at the present time.

## 4. Mutagenicity and Cell Transformation

The mutagenic potential of chloroprene was assessed from an evaluation of 10 studies (Table 3): one host-mediated, two *in vitro*, four whole animal, and three human cytogenetic (workplace exposure). The majority of these studies yielded positive results in the presence of metabolic activation, indicating that chloroprene is a promutagen—i.e., chloroprene requires metabolic activation to exhibit a positive mutagenic response. The low level of mutagenicity observed in the *Salmonella* histidine reversion assay in the absence of an exogenous S9 activation system may have been due to bacterial metabolism of chloroprene. The potentially mutagenic metabolites are probably generated by epoxidation of a double bond. (Bartsch et al., 1979).

Chloroprene was determined to be mutagenic in the sex-linked recessive lethal test in *Drosophila* (Vogel, 1976, 1979). Thus chloroprene caused heritable effects in the fruit fly. Additional information, particularly from well-designed studies in mammals, is necessary before any conclusions can be made regarding the potential of chloroprene to cause heritable effects in man.

Chloroprene has also been found to cause chromosomal aberrations in cultured lymphocytes of humans exposed in the workplace (Katosova, 1972). Suggestive evidence for chromosomal effects was also found in bone marrow cells of mice exposed *in vivo* (Sanotskii, 1976). In addition, chloroprene was reported to be positive in the dominant lethal test in rats and mice (Sanotskii, 1976). These results suggest that chloroprene is a clastogen.

In summary, the weight of the available evidence suggests that chloroprene is a mutagen and a clastogen and transforms cells *in vitro*. Positive results were obtained (see Table 3) in bacteria, *Drosophila*, mice, rats, and humans (chromosome aberration studies). Negative results were reported for mammalian cells in culture, but chloroprene transformed hamster cells *in vitro* as indicated by tumors following transplantation of the cells (Menezes et al., 1979).

**Table 3. Studies of Mutagenic Potential of Chloroprene**

| Type of Study | Organism | Chloroprene Concentration | Effects | Reference |
|---|---|---|---|---|
| In Vitro | S. typhimurium | 8% vapor in air | 3x increase in revertants (8x w/S9) | Bartsch et al., 1979 |
| In Vitro | V79 Chinese hamster cells | (dose?) | Negative in presence of S15 | Drevon and Kuroki, 1979 |
| Host-mediated | Mouse, S. typhimurium | 750 mg/kg<br>375 mg/kg | 214 mutations/1 x 108 cells<br>71 mutations/1 x 108 cells | Fichidzhyan et al., 1976 |
| Whole animal | D. melanogaster | 11.4 mM in food<br>5.7 mM in food | 1.0 ± 0.4% recessive lethals<br>0.58 ± 0.3% lethals<br>(control 0.18 ± 0.4%) | Vogel, 1976 |
| Whole animal | D. melanogaster | 5.7-34.3 mM | Pooled data were positive at 1% significance | Vogel, 1979 |
| Whole animal | Mouse | 3.5 mg/m$^3$ in air for 20 mo. | Increase in chromosomal aberrations | Sanotskii, 1976 |
| Whole animal | Rat | 0.14 mg/m$^3$ for 2.5 mo. | Dominant lethals | Sanotskii, 1976 |
| Whole animal | Mouse | 0-3.5 mg/m$^3$ | Dose-related increase in dominant lethals | Sanotskii, 1976 |
| Human | Cultured lymphocytes | 18 mg/m$^3$ for 2-10 yrs. | 4.77 ± 0.57% chromosomal aberrations compared to 0.65 ± 0.50% in controls | Katosova, 1972 |
| Human | Cultured lymphocytes | 3-7 mg/m$^3$ in air | 3.49 ± 0.51% chromosomal aberrations compared to 1.19 ± 0.06% in controls | Sanotskii, 1976 |
| | | 1-4 mg/m$^3$ in air | 2.5 ± 0.49% chromosomal aberrations compared to 1.19 ± 0.06% in controls | |

# IV. SUMMARY AND CONCLUSIONS

The potential for the release of chloroprene to the environment exists during its manufacture, transport, and storage, and during the manufacture of polychloroprene elastomers and polychloroprene-containing products. Little information is currently available regarding levels of chloroprene in the environment resulting from any of these processes.

The ultimate environmental fate of chloroprene depends on its release, transport, and persistence. Chloroprene is not expected to persist in the environment or bioaccumulate due to its high reactivity. If released into the atmosphere, its estimated half-life is measured in hours. If released at the soil/air or water/air interface, chloroprene's volatility indicates that it will partition into the air. Due to its relatively low soil sorption and substantial water solubility (from an environmental perspective), release of chloroprene at the soil/water interface is likely to result in its partitioning into aqueous compartments. Reactivity with soil constituents is another possibility.

In occupationally exposed workers, chloroprene has been reported to cause respiratory, skin, and eye irritation, temporary hair loss, dizziness, insomnia, headache, and fatigue. Clinical signs of toxicity have been reported for liver, circulatory system, hematopoietic, central and peripheral nervous systems, immune system, reproductive system, and periodontium. Studies in animals have indicated that exposure to high levels of chloroprene by inhalation, gavage, or subcutaneous injection adversely affects the liver, lungs, kidneys, and central nervous system. The effects included vascular congestion, hepatic centrilobular necrosis and degeneration of the renal tubular epithelium, edema of the lungs, CNS depression, and mortality. The results of two studies have indicated that chloroprene suppresses immune system function; another study reported histopathologic effects in the adrenal gland and anterior pituitary after 6 months of inhalation exposure to chloroprene. Insufficient data were available to identify levels at which subchronic or chronic exposures would produce no systemic toxicity. The data for subchronic exposures are limited.

Several cytogenetic studies of chromosomal aberrations in occupationally exposed men and women in the U.S.S.R. have indicated that chloroprene may be mutagenic. There is evidence from *in vivo* and *in vitro* tests that chloroprene is mutagenic and clastogenic. Positive results have been found in bacteria, *Drosophila*, mice, and rats. Chloroprene also showed malignant transformation *in vitro* with an established normal hamster lung cell line.

An epidemiologic study conducted in the U.S.S.R. has provided evidence suggesting that chloroprene is related to increased incidences of lung and skin cancer. Results from more recent studies of U.S. chloroprene workers, provided some evidence of a slightly increased lung cancer risk. While the findings of the American studies are similar to the Soviet studies with regard to lung cancer risk, serious limitations in all of the cancer epidemiologic studies preclude any definite conclusions.

Tumorigenic effects of chloroprene have been studied in mice following skin application and in rats by oral, subcutaneous, and intratracheal administration. No (or inconclusive) tumorigenic effects were found. However, the compound was reported to increase the rate of tumor growth of transplanted tumor cells possibly due to immunosuppression. None of these studies is adequate for evaluating the carcinogenicity of chloroprene in experimental animals, as they lacked adequate durations of exposure; the experimental details reported were not adequate. According to the criteria of the International Agency for

Research on Cancer (IARC), the weight of both human and animal evidence for the carcinogenicity of chloroprene should be categorized as very limited or inadequate at the present time. The overall evaluation of chloroprene, based on IARC criteria, places it in Group 3, meaning that the chemical cannot be classified as to its carcinogenicity for humans.

However, it should be noted that 1,3-butadiene, a non-chlorinated analog of chloroprene, has been shown to be carcinogenic in mice and rats. This structure-activity relationship and the mutagenic and cell-transforming capability of chloroprene suggests that chloroprene could be carcinogenic and should, therefore, be tested further.

No data exist which can be used for the quantitative estimation of the potential human health effects, including carcinogenicity, of chloroprene.

## REFERENCES


Agadzhanov, M. I.; Melik-Agayan, E. A.; Michitaryan, V. G. (1973) Effect of organic peroxides on lipid peroxide dynamics in tissues. Biol. Zh. Arm. 26:28-34. [cited in Haley, 1978].

Agakhanyan, A. G. (1982) Aspects of the effect of several alkylating and organochlorine hydrocarbons on immunocompetent lymphoid tissue. Zh. Eksp. Klin. Med. 22:28-31.

Airapetyan, A. A.; Matevosyan, M. S. (1973) Effect of chloroprene poisoning on internal inhibition processes in albino rats. Biol. Zh. Arm. 26:11-18.

Anonymous. (1981) World: synthetic rubber capacity, 1979 (000m tons). Mater. Plast. Elastomeri (May): 288.

Aznauryan, A. V.; Erznkatsyan, M. P.; Aznauryan, A. S. (1981) Several pathomorphological changes in rat organs during chronic chloroprene intoxication along with nutritive rations of varying protein levels. Zh. Eksp. Klin. Med. 21: 136-140.

Bartsch, H. (1977) Vinyl chloride (VCM): an example for evaluating adverse biological effects in short-term tests. Mutat. Res. 46:200-201.

Bartsch, H.; Malaveille, C.; Barbin, A.; Planche, G. (1979) Mutagenic and alkylating metabolities of halo-ethylenes, chlorobutadienes and dichlorobutenes produced by rodent or human liver tissues. Evidence for oxirane formation by P450 linked microsomal monooxygenase. Arch. Toxicol. 41:249-277.

Clary, J. J.; Feron V. J.; Reuzel, P. G. J. (1978) Toxicity of beta-chloroprene (2-chlorobutadiene-1,3). Acute and subacute toxicity. Toxicol. Appl. Pharmacol. 46:375-384.

Cote, Ila (1985) Noncarcinogenic effects of chloroprene. Memo. Office of Air Quality Planning and Standards, U.S. EPA.

Culik, R.; Kelly, D. P.; Clary, J. J. (1978) Inhalation studies to evaluate the teratogenic and embryotoxic potential of beta-chloroprene (2-chlorobutadiene-1,3). Toxicol. Appl. Pharmacol. 44:81-88.

Cupitt, L. T. (1980) Fate of toxic and hazardous materials in the air environment. Research Triangle Park, NC: U.S. Environmental Protection Agency, Environmental Sciences Research Laboratory; EPA report no. EPA-600/3-80-084. Available from NTIS, Springfield, VA; PB80-221948.

Davtyan, R. M. (1972) Toxicological characteristics of the action of chloroprene on the reproductive function of male rats. In: Toksikologiya i gigiena produktov neftekhimii i neftekhimicheskikh proizvodstv, vsesoyuznaya konferentsiya, (doklady) 2nd [Toxicology and hygiene of the products of petroleum chemistry and petrochemical productions, 2nd all-union conference, (reports)]; 1971; Yaroslavl, USSR. Yaroslavl, USSR: Yaroslavskii Meditsinskii Institut; pp. 95-97.

Dilling, W. L. (1977) Interphase transfer processes. II. Evaporation rates of chloromethanes, ethanes, propanes, and propylene from dilute aqueous solutions. Comparisons with theoretical predictions. Environ. Sci. Technol. 11:405-409.

Drevon, C.; Kuroki, T. (1979) Mutagenicity of vinyl chloride, vinylidene chloride and chloroprene in V79 Chinese hamster cells. Mutat. Res. 67:173-182.

Federal Register (1984) Rationale for recommendations. 49: 46938.

Fichidzhyan, B. S.; Zil'fyan V. N. (1976) Immunological reorganization of white rats under the effect of chloroprene. Zh. Eksp. Klin. Med. 16: 43-46.

Fichidzhyan, B. S.; Rybakova, K. D.; Lokashina, S. Y. (1976) Results of a study of the mutagenic action of chloroprene on microorganisms. Zh. Eksp. Klin. Med. 16: 39-41.

Gooch, J. J.; Hawn, W. F. (1981) Biochemical and hematochemical evaluation of chloroprene workers. J. Occup. Med. 23: 268-272.

Haley, T. J. (1978) Chloroprene (2-chloro-1,3-butadiene)—what is the evidence for its carcinogenicity? Clin. Toxicol. 13:153-170.

Henkson, R. (1985) [Telephone communication with Dr. Ila Cote.] Houston, TX. Denka Chemical Co.

International Agency for Research on Cancer. (1979) Chloroprene and polychloroprene. In: Some monomers, plastics and synthetic elastomers, and acrolein. Lyon, France: World Health Organization; pp. 131-156. (IARC monographs on the evaluation of the carcinogenic risk of chemicals to humans: v.19).

Katosova, L. D. (1973) Cytogenic analysis of peripheral blood of workers engaged in production of chloroprene. Gig. Tr. Prof. Zabol. 17:30-32.

Khachatryan, E. A. (1972a) Lung cancer morbidity among persons working with chloroprene. Vopr. Onkol. 18:85-86.

Khachatryan, E. A. (1972b) The role of chloroprene compounds in the induction of neoplasms of the skin. Gig. Tr. Prof. Zabol. 16:54-55.

Leet, T. L.; Selevan, S. G. (1982) Mortality analysis of workers exposed to chloroprene. Cincinnati, OH: Department of Health and Human Services, National Institute for Occupational Safety and Health. Available from: NTIS, Springfield, VA; PB83-193581.

Markaryan, L. P.; Shakhlamov, V. A. (1975a) Ultrastructure of cells in the anterior pituitary of albino rats with chronic intoxication by chloroprene vapors. Biol. Zh. Arm. 28:35-38.

Markaryan, L. P.; Shakhlamov, V. A. (1975b) Ultrastructure of the adrenal cortex of white rats under chronic chloroprene intoxication. Zh. Eksp. Klin. Med. 15:27-31.

Menezes, S.; Padadopoulo, D.; Levy, S.; Markovits, P. (1979) In vitro transformation of lung cells of young hamsters by chloro-2-butadiene. C.R. Hebd. Seances Acad. Sci. Ser. D 288:926-929.

Nystrom, A. E. (1948) Health hazards in the chloroprene rubber industry and their prevention. A clinical and experimental study with special reference to chloroprene as well as oxidation and polymerization products thereof. Acta Med. Scand. 132 (suppl. 219):1-125.

Pell, S. (1978) Mortality of workers exposed to chloroprene. J. Occup. Med. 20: 21-29.

Pell, S. (1980) A cohort mortality study of workers exposed to chloroprene at the Louisville Works. Unpublished draft supplied by: H. E. Serenbetz, DuPont Co., Wilmington, DE.

Pellizzari, E. D.; Erickson, M. D.; Zweidinger, R. A. (1979) Formulation of a preliminary assessment of halogenated organic compounds in man and environmental media. Washington, DC: U.S. Environmental Protection Agency; EPA report no. EPA-560/13-79/006. Available from: NTIS, Springfield, VA; PB80-112170.

Ponomarkov, V.; Tomatis, L. (1980) Long-term testing of vinylidene chloride and chloroprene for carcinogenicity in rats. Oncology 37:136-141.

Salnikova, L. S.; Fomenko, V. N. (1973) Experimental study of the effect of chloroprene on embryogenesis. Gig. Tr. Prof. Zabol. 17:23-26.

Sanotskii, I. V. (1976) Aspects of the toxicology of chloroprene: immediate and long-term effects. Environ. Health Perspect. 17:85-93.

Serenbetz, H. (1985) [Telephone communication with Mr. William Ewald]. May. Wilmington, DE: E.I. DuPont de Nemours Co.

Shukuryan, S. G. (1967) Vopr. Rentgenol. Onkol., Akad. Nauk Arm. SSR. 7:205. [cited in Haley, 1978.]

Summer, K. H.; Greim, H. (1980) Detoxification of chloroprene (2-chloro-1, 3-butadiene) with glutathione in the rat. Biochem. Biophys. Res. Commun. 96:566-573.

Vogel, E. (1976) Mutagenicity of carcinogens in *Drosophila* as a function of genotype-controlled metabolism. In: deSerres, F. J.; Fouts, J. R.; Bend, J. R.; Philpot, R. M., eds. *In vitro* metabolic activation in mutagenesis testing. Amsterdam, The Netherlands: Elsevier/North-Holland Biomedical Press; pp. 63-79.

Vogel, E. (1979) Mutagenicity of chloroprene, 1-chloro-1,3-trans-butadiene, 1,4-dichlorobutene-2 and 1,4-dichloro-2-3-epoxybutane in *Drosophila melanogaster*. Mutat. Res. 67:377-381.

Volkova, Z. A.; Fomenko, V. N.; Bagdinov, Yu. M.; Byalko, N. K.; Katosova, L. D.; Ponomareva, N. I.; Tolcheva, E. I.; Davtyan, R. M.; Zil'fyan, Z. N.; Gurdzhiyev, T. I.; Khaprullina, A. Sh. (1976) Determination of the maximum permissible concentrations of chloroprene in the air of working areas. Gig. Tr. Prof. Zabol. 3:31-36.

Ward, J. B., Jr.; Whorton, E. B.; Gilmer, P. R., Jr.; Schoen, I. (1981) Liver function among neoprene production workers. Galveston, TX: Texas University Medical Branch. Available from: NTIS, Springfield, VA; PB82-231044.

Zil'fyan, V. N.; Fichidzhyan, B. S. (1972) Effect of chloroprene on development of Crocker's murine sarcoma. In: Materialy nauchnoi konferentsii, posvyashchennoi 50-letiyu obrazovaniya SSSR i 25-letiyu organizatsii Armyanskogo Instituta Rentgenologii i Onkologii [Materials of the scientific conference celebrating the fiftieth anniversary of the formation of USSR and the twenty-fifth anniversary of the Armenian Institute of Roentgenology and Oncology]; Yerevan, USSR. Yerevan, USSR: Armyanskii Institut Rentgenologii Onkologii; pp. 105-106.

Zil'fyan, V. N.; Fichidzyhan, B. S.; Pogosova, A. M. (1975) Results of testing chloroprene for carcinogenicity Zh. Eksp. Klin. Med. 15:54-57.

Zil'fyan, V. N.; Fichidzyhan, B. S.; Garibyan, D. K.; Pogosova, A.M. (1977) Experimental study of chloroprene for carcinogenicity Vopr. Onkol. 23:61-65.